## REMARKS

Claims 1 – 26 are currently pending in the application. New claim 27 has been added.

### *Claim Rejections – 35 USC 112*

Claims 1-4, 6-12 and 14-26 are rejected under 35 USC 112 second paragraph as being indefinite. Claims 1, 12, 19, and 25 have been amended in accordance with the Examiner's requirements.

### *Claim Rejections – 35 USC 102*

Claims 19-23 have been rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Comanor, US 5,860,917.

Reconsideration of the above-identified claims in view of the amendments above and the remarks following is respectfully requested.

Comanor discloses evaluating the response of a patient having a disease to a therapeutic regimen for the disease. Correlations between observed phenomena and one or more factors are used to predict the likelihood of particular patient showing a desired response to treatment.

As far as the mathematical model is concerned the description in Comanor is generic to any predictive model that exists. That is to say, Comanor is interested in the application of predictive models in general to treatment efficacy.

Furthermore, Comanor considers a specific case in which he predicts efficacy of the treatment using ALT and AST as response measurements. He considers in particular ratios for each of the enzymes separately of enzyme level change over a one month time interval. By contrast, the model of the present invention as claimed in claim 19 considers a specific model structure in which ALT and AST absolute levels serve as inputs, and both the absolute levels *and* ratios therebetween are used in a structure involving a series of nodes. Data mining is then used (the predictor) between the nodes to determine over a large statistical sample how to configure the output to provide a prediction of toxicity.

That is to say the claim covers a specific predictive answer for a given patient obtained through use of a specific prediction mechanism, and not a general prediction involving the treatment. The Comanor disclosure shows a very limited type of

statistical model in which the inputs are either used directly or are processed in a way which is predefined. In the present invention the predictor actually finds the best way, based on statistical insight, to process the inputs in order to arrive at the prediction. Claim 19 has therefore been amended to recite that the predictor includes a statistical model to which the various levels and ratio can be applied.

Comanor in fact makes direct, that is non-statistical, use of a very specific input. As shown in Col 16 line 16, the ratio used is specifically a normalized natural log of the ratio for a single enzyme of the natural log at Time A to the ratio of the natural log at Time B. There is no disclosure of use of a ratio between both enzymes and in fact it appears from equation 9, (col. 17 line 35) that use of values of AST were in fact excluded by the processing. Thus in fact not only does Comanor not teach the combined ratio of AST and ALT of claim 19, it in fact leads directly away from inclusion of AST in the first place.

By contrast the present application provides (page 15 line 15 ff) "The processor preferably also includes analysis, or predictor, functionality which uses either or both of the absolute values and the ratio between to decide on the potential for liver toxicity. For example the predictor may be set to conclude from low ALT and AST levels and departure from the linear relationship, that a likelihood of development of liver toxicity is low. Likewise the predictor may be set to conclude from high ALT and AST levels, that a likelihood of liver toxicity is relatively high. Again, the predictor may be set to conclude from departure from linearity, without reference to absolute levels, that a likelihood of liver toxicity is relatively high. Likewise, the predictor may be set to conclude from a ratio close to linearity, without reference to absolute levels, that a likelihood of liver toxicity is relatively low. In a preferred embodiment, a thresholder may be included in the predictor for setting a threshold likelihood, above which application of the pharmaceutical substance is to be discontinued as being too dangerous. The threshold is preferably altered for different substances and for different ailments. For example a drug being used in a life-threatening ailment is preferably assigned a high threshold for discontinuity whereas a drug that is being used for a chronic but low level condition may be given a lower threshold for discontinuity."

It is thus submitted that claims 19- 23 are both novel and non-obvious in light of Comanor, and that the rejection of the Examiner has been overcome.

***Claim Rejections – 35 USC 103***

Claims 1-4, 6-12, 14-18 and 25 have been rejected under 35 U.S.C. § 103(a) as being rendered obvious over Staub in view of Seilhamer. Reconsideration of the above-identified claims in view of the amendments above and the remarks following is respectfully requested.

Claim 1 has been restricted to recite that the model provides predictions of future states of the system. A corresponding amendment has been made to claim 12.

Staub discloses computer systems that automatically generate knowledge bases to create logical trees including a graphic relationship between the nodes.

Staub describes software to be used by an expert to create a decision tree, which describes alternative options and decision points. That is to say, having done X, go on to Y if A applies, otherwise go on to B. See Staub Fig. 4 where a simplified procedure for carrying out diagnostics on an electronic device is shown. By contrast with Staub, the model of the present invention is not a decision tree, rather an influence map – a description of what factors play a role in the outcome of interest. Relationships are statistical. The terms used by Staub, such as nodes and legs are not relevant to the present invention.

Seilhamer describes a methodology to test biological entities, such as liver cells, with drugs knowing the drug toxicity, in order to determine gene expression. In the methodology, differentiation of cells is carried out using gene transcript frequency analysis. Differentiation involves comparison between cells treated by the drug. Seilhamer fails to provide a definition of a series of model states and a data miner for investigation of relationships between those states in order to predict toxicity. Seilhamer rather determines actual toxicity by direct examination of the cell. The whole point of Seilhamer is to apply the same drug levels to the cells, and the user can then make determinations about the genes from the gene transcript profile. As is clear from the description in column 20 it is direct examination of the cell that determines toxicity. There is no suggestion in Seilhamer to apply any kind of model in order to *predict* toxicity in a cell that has not been examined.

Furthermore there is no teaching by Seilhamer to go beyond the cell to predict toxicity in a human, and to end, a new claim 27 is added directed to the biological entity being a macro-biological entity.

It is therefore respectfully suggested that none of the claims are taught or suggested by the combination of Seilhamer and Staub.

All of the rejections raised by the Examiner are believed to have been overcome, either by the above amendments or by the above arguments.

In view of the foregoing, it is submitted that all the claims now pending in the application are allowable over the cited reference. An early Notice of Allowance is therefore respectfully requested.

Respectfully submitted,

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